Genes, Lifestyles, and Crossword Puzzles:

Can Alzheimer's Disease be Prevented?





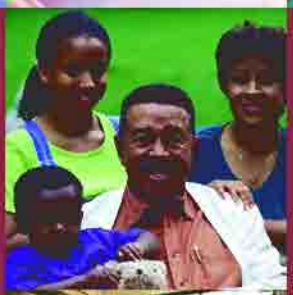

TABLE OF CONTENTS

Introduction

These days, it seems that newspapers, magazines, and TV are full of stories about ways to stay healthy, eat right, and keep fit. Lots of people are concerned about their health as they get older. They wonder whether they can do anything to prevent diseases that happen more often with age, such as Alzheimer's disease (AD).

AD has no known cure, and the secrets to preventing it are not yet known. But research supported by the National Institute on Aging (NIA) and other public and private agencies offers tantalizing clues about the origins and development of AD. These findings are raising hopes that someday it might be possible to delay the onset of AD, slow its progress, or even prevent it altogether. Delaying by even 5 years the time when AD symptoms begin could greatly reduce the number of people who have the disease.

Preventing a Complex Disease Like AD is a Challenge

Many diseases, such as diabetes, heart disease, and arthritis, are complex. They develop when genetic, environmental, and lifestyle factors work together to cause a disease process to start and then progress. The importance of these factors may differ for each person. AD is one of these complex diseases. It develops over many years, and it appears to be affected by a number of factors that may increase or decrease a person's risk of developing the disease. We don't have control over some of the risk factors for AD; we can do something about other possible AD risk factors, though.

Learning About AD Risk Factors We Can't Control

Age is the most important known risk factor for AD. The risk of developing the disease doubles every 5 years over age 65. Several studies estimate that up to half the people older than 85 have AD. These facts are significant because of the growing number of people 65 and older. More than 34 million Americans are now 65 or older. Even more significant, the group with the highest risk of AD—those older than 85—is the fastest growing population group in the country.

Genetics is the other known AD risk factor that a person can't control. Scientists have found genetic links to the two forms of AD. Early-onset AD is a very rare form of the disease that can occur in people between the ages of 30 and 60. In the 1980s and early 1990s, researchers found that mutations (or changes) in certain genes on three chromosomes cause early-onset AD. A person has a 50-50 chance of developing early-onset AD if one parent has any of these genetic mutations.

Late-onset AD, the more common form, develops after age 65. In 1992, researchers found that certain forms of the apolipoprotein E (APOE) gene can influence AD risk:

- APOE ε2, a rarely occurring form, may provide some protection;
- APOE ε3, the most common form, appears to play a neutral role; and
- APOE ε4, which is found in about 40 percent of people with AD, appears to increase risk. (Having this gene form does not mean that a person will definitely develop AD; it only increases risk. And, many people who develop AD do not have an APOE ε4 gene.)

Researchers are now intensively searching for other risk factor genes that may be linked to late-onset AD. Discovering these genes is essential for understanding the causes of AD and pinpointing targets for drug development and other prevention or treatment strategies. It's also critical for developing better ways to identify persons at risk.

In 2003, NIA announced a major expansion of AD genetics research efforts. The AD Genetics Study is collecting genetic material from individuals in families with two or more living brothers or sisters who have late-onset AD. This valuable resource will allow geneticists to speed up the discovery of additional AD risk factor genes.

The Search for AD Prevention Strategies

Though we can't do much about our age or genetic profile, recent research suggests that maintaining good overall health habits may help lower the chances of developing several serious diseases, including AD. Scientists are studying a number of health, lifestyle, and environmental factors that could make a difference. Many of these potential factors have been identified in observational and animal studies, and at present, they are only associated with changes in AD risk. Only further research, including clinical trials, will reveal whether, in fact, these factors can help to prevent AD.

Investigating heart disease risk. In recent years, basic research in laboratories as well as population and animal studies have suggested a connection between AD risk and high levels of cholesterol in the blood. These findings led scientists to wonder whether drugs that lower blood cholesterol might also lower the risk of developing symptoms associated with dementia and AD. Two recent population studies have raised the possibility that people who take statins, the most commonly prescribed cholesterol lowering drugs, may have reduced risk of dementia.

Other studies, though, have found no association between statins and dementia risk. Thus it is not clear at this time from population studies whether statins do or do not prevent AD.

Other research has found that a high level of the amino acid homocysteine is associated with an increased risk of developing AD. High levels of homocysteine are known to increase heart disease risk, and NIA studies in mice have shown that high levels of this amino acid can make neurons stop working and die. The relationship between AD risk and homocysteine levels is particularly interesting because blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B6 and B12.

Examining high blood pressure. There also are associations among AD, high blood pressure that begins in midlife, and other risk factors of stroke. It is known that even in relatively healthy older adults, high blood pressure and other stroke risk factors, such as age, diabetes, and cardiovascular disease, can damage blood vessels in the brain and reduce the brain's oxygen supply. This damage may disrupt nerve cell circuits that are thought to be important to decision-making, memory, and verbal skills. Scientists are studying the connections between AD and high blood pressure in hopes that knowledge gained will provide new insights into both conditions.

Learning about diabetes and insulin resistance. Large-scale population studies suggest that diabetes is associated with several types of dementia, including AD and vascular dementia (a type of dementia associated with strokes). These studies have found that AD and type 2 diabetes share several characteristics, including increasing prevalence with age, genetic predisposition, and

deposits of two different kinds of damaging amyloid protein (in the brain for AD and in the pancreas for type 2 diabetes). Abnormal glucose regulation, a key element of diabetes, may also be involved in AD.

Scientists are learning more about the possible relationships between AD and diabetes. For example, since 1993, scientists funded by NIA have been working with a large group of older priests, nuns, and brothers in a research project called the Religious Orders Study (ROS). This study has provided a wealth of information about many aspects of AD, including the possible link between diabetes and cognitive decline. In one analysis involving more than 800 participants, researchers examined tests of five "cognitive systems" involved with word and event memory, information processing speed, and the ability to recognize spatial patterns. The researchers found a 65 percent increase in the risk of developing AD among those with diabetes compared with those who did not have diabetes. They also found that diabetes was related to declines in some cognitive systems but not others.

Researchers also are becoming increasingly interested in the possible role of insulin resistance (a condition in which the body produces insulin but cells do not use it properly) in AD. Too much insulin in the blood (which happens as a result of insulin resistance) may encourage inflammation and oxidative stress, both of which contribute to the damage seen in AD. Scientists are testing several drugs used to treat diabetes to see whether they can improve AD symptoms or slow the progression of AD.

Exploring intellectually stimulating activities. Studies have shown that keeping the brain active is associated with reduced AD risk. In the Religious Orders Study, for example, investigators periodically asked more than 700 participants to describe the amount of time they spent in seven activities that involve significant information processing. These activities included listening to the radio, reading newspapers, playing puzzle games, and going to museums. After following the participants for 4 years, investigators found that the risk of developing AD was 47 percent lower on average for those who did the activities most frequently than for those who did them least frequently. Studies similar to the ROS study have shown similar results. In addition, a growing body of research, including other findings from this group, suggests that, even in the presence of AD plaques, the more formal education a person has, the better his or her memory and learning ability.

Another NIA-funded study also supports the value of lifelong learning and mentally stimulating activity. In this study of healthy older people and people with possible or probable AD, scientists found that during their early and middle adulthood, the healthy older people had engaged in more of those mentally stimulating activities and spent more hours engaged in them than did those who ultimately developed AD.

The reasons for these types of findings aren't entirely clear, though scientists have come up with four possibilities:

- It may be that these activities protect the brain in some way, perhaps by establishing a "cognitive reserve."

- Perhaps these activities help the brain become more adaptable and flexible in some areas of mental function so that it can compensate for declines in other areas.

- A third possibility is that a lower level of engagement in intellectual stimulation could reflect very early effects of the disease.

- Finally, perhaps people who engage in these activities have other lifestyle features that may protect them against developing AD.

The only way to really evaluate these possibilities is by testing them in a more controlled way in a clinical trial.

Several clinical trials have directly examined whether memory training and similar types of mental skills training can actually improve the cognitive abilities of healthy older adults and people with mild AD. In the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, certified trainers provided 10 sessions of memory training, reasoning training, or speed of processing training to healthy adults 65 years old and older. The sessions improved participants' mental skills in the area in which they were trained. Even better, these improvements persisted for 2 years after the training was completed. In another study, 25 participants with mild AD worked with researchers to learn how to improve their ability to carry out various tasks, such as how to associate names and faces, recall the names of objects, and pay bills correctly. Compared to another group with mild AD who received more generic mental stimulation activities, people in the "cognitive rehabilitation" group improved their abilities more, and their abilities were still improved 3 months later.

Investigating physical activity. Accumulating evidence suggests that being physically active may benefit more than just our hearts and waistlines. Research in animals has shown that both physical and mental function improve with aerobic fitness. Two studies in aging adults have shown similar results. The first study used magnetic resonance imaging (MRI) to measure changes in brain activity in healthy adults aged 58-78 before and after a 6-month program of brisk walking. The researchers found that improvements in the participants' cardiovascular fitness resulted in increased functioning in certain regions of the brain. Compared to a physically inactive group, the walkers were able to pay attention better and focus more clearly on goals while disregarding unimportant information. In an observational study, investigators studied the relationship of physical activity and mental function in nearly 6,000 healthy women 65 years old and older over a period of up to 8 years. The investigators found that the women who were more physically active were less likely to experience a decline in their mental function than were inactive women.

Scientists have speculated about why physical activity may help our brains as much as our bodies. It may be that physical activity improves blood flow to the brain so that it responds better to a task or that it activates cellular mechanisms that improve brain function.

Examining nonsteroidal anti-inflammatory drugs (NSAIDs). Inflammation of tissues in the brain is a common feature of AD, but it is not clear whether it is a cause or effect of the disease. Some population studies suggest an association between a reduced risk of AD and NSAIDs, such as ibuprofen, naproxen, and indomethacin. Clinical trials thus far have not demonstrated

a benefit for AD from these drugs or from the newer cyclooxygenase-2 (COX-2) inhibitors, such as rofecoxib and celecoxib. A trial testing whether naproxen or celecoxib could prevent AD in healthy older people at risk of the disease has been suspended, but investigators are continuing to conduct follow-up examinations with participants and to examine data about cognitive changes and possible cardiovascular risk. Scientists are interested in modifying the brain inflammatory processes associated with AD, and they continue to look for ways to test how particular anti-inflammatory drugs might affect the development or progression of AD.

Learning about antioxidants. Another promising area of research focuses on highly-active molecules called free radicals. Damage from these free radicals during aging can build up in nerve cells and result in a loss of cell function, which could contribute to AD. Some population and laboratory studies suggest that antioxidants from dietary supplements or food may provide some protection against this damage (called oxidative damage), but other studies show no effect. Clinical trials may provide some answers. Several trials are investigating whether two antioxidants—vitamins E and C—can slow cognitive decline and development of AD in healthy older individuals. The NIA is conducting a clinical trial that will examine whether taking vitamin E and/or selenium supplements over a period of 7 to 12 years can help prevent memory loss and dementia. This trial is an add-on to a prostate cancer prevention clinical trial funded by the National Cancer Institute (NCI). Another just-completed study focused on the use of vitamin E in people with mild cognitive impairment (MCI). MCI is a type of memory change that is different from both AD and normal age-related

memory change. People with MCI have ongoing memory problems, but they do not have other losses like confusion, attention problems, and difficulty with language. This NIA study, the Memory Impairment Study, compared donepezil (Aricept), vitamin E, or placebo in participants with MCI to see whether the drugs might delay or prevent progression to AD. The study found that taking vitamin E had no effect on progression to AD at any time in the study when compared with placebo. It may be that this antioxidant may not help after memory declines have already started. Donepezil, however, did seem to delay progression to MCI over the first year of treatment.

Expanding knowledge about estrogen. This hormone is produced by a woman's ovaries during her childbearing years. After this time, estrogen production declines dramatically. Over the past 25 years, some laboratory and animal research, as well as observational studies in women, have suggested that estrogen used by women to treat the symptoms of menopause also protects the brain, and experts have wondered whether using estrogen could reduce the risk of AD or slow the disease.

However, clinical trials testing this approach on postmenopausal women have found that using estrogen to treat or prevent AD may not be effective. A number of clinical trials have showed that estrogen does not slow the progression of already-diagnosed AD. A large trial found that women older than 65 who took estrogen (Premarin) alone or estrogen with a synthetic progestin were actually at increased risk of developing dementia, including AD. Concurrently, researchers have tried other avenues to capitalize on estrogen's potentially positive effects for the brain. For example, scientists have developed estrogen-like molecules

called SERMs (selective estrogen-receptor modulators). These molecules may retain estrogen's neuron-protecting ability but may not have some of its other harmful effects on the body. A large clinical trial tested a SERM called raloxifene, which is used in the prevention and treatment of osteoporosis. The study showed that this SERM lowered the risk of MCI among this group of postmenopausal women with osteoporosis.

Investigating *ginkgo biloba*. This readily available natural product has been proposed as a potential treatment or preventive agent for AD. Although a 1997 study in the U.S. suggested that a ginkgo extract may be of some help in treating the symptoms of AD and vascular dementia, there is no evidence that *ginkgo biloba* will prevent AD. At the NIH, the National Center for Complementary and Alternative Medicine and NIA are currently supporting a large clinical trial to explore whether ginkgo has any effect on preventing AD or delaying cognitive decline in older adults.

Exploring immunization. Will a vaccine someday prevent AD? Early vaccine studies in mice were so successful in reducing deposits of beta-amyloid (the major component of the plaques that develop in the brains of people with AD) and improving brain performance on memory tests that investigators conducted preliminary clinical trials in humans with AD. These studies had to be stopped because of side effects that occurred in some participants. However, research on this strategy is continuing in animals and humans and is helping to clarify the AD disease process.

Understanding social engagement. Evidence from studies of animals, nursing home residents, and community-dwelling older people has suggested a link between social engagement and cognitive performance. Older adults who have a rich social network and participate in many social activities tend to have reduced cognitive decline and decreased risk of dementia. In the NIA-funded Chicago Health and Aging Project, a high level of social engagement was associated with a significant reduction in cognitive decline. More research is needed to understand why social ties may have a protective effect. For example, is it simply because lifestyles that involve much social interaction and diverse social activities are cognitively challenging? Or, do these lifestyles contribute in some other way to brain reserve?

The Search for Other Clues That May Contribute to Prevention Strategies

Investigators also are trying to discover whether changes in certain biological compounds in blood, urine, or cerebrospinal fluid could indicate early AD changes in the brain. Understanding more about these biological markers, how they work, and what causes their levels to change, is important to help scientists answer questions about what makes AD begin and develop. Learning more about these markers also may help scientists track whether certain therapeutic compounds are having their intended effects and may some day lead to new prevention strategies.

One major effort involves the use of imaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), to measure brain structure and function. An NIA public-private partnership—the AD Neuroimaging

Initiative—is a large study that will determine whether MRI and PET scans or other imaging or biological markers can be used to identify early AD changes and disease progression. One day, these measurements may be able to identify those people who are at risk of AD before they develop symptoms as well as help physicians assess the response to treatment. To learn more about the Neuroimaging Initiative, visit NIA's Alzheimer's Disease Education and Referral Center (ADEAR) at *www.alzheimers.org* or call ADEAR toll-free at 1-800-438-4380.

What Can You Do?

Our knowledge is growing rapidly as scientists expand their understanding of the many factors involved in the development of AD. Even though no treatments, drugs, or pills have been proven to completely prevent AD, people can take some actions that might reduce the effect of possible AD risk factors. These actions include:

- lowering cholesterol and homocysteine levels
- lowering high blood pressure levels
- controlling diabetes
- exercising regularly
- engaging in intellectually stimulating activities

All of these strategies are good to do anyway because they lower risk for other diseases and help maintain and improve overall health and well-being. However, it is important to

remember that pursuing any of these strategies will not necessarily prevent or delay AD in any one individual. Even if the strategies were eventually proven to be effective, they might not offset a person's individual genetic and other risk factors enough to prevent AD from developing.

Another important action a person can take is to join the Genetics Study, the Neuroimaging Initiative, or an AD clinical trial. People who participate in these kinds of studies say that the biggest benefit is having regular contact with experts on AD who have lots of practical experience and a broad perspective on the disease. They also feel they are making a valuable contribution to knowledge that will help people in the future who develop AD. Families interested in participating in the Genetics Study can call the National Cell Repository for Alzheimer's Disease (NCRAD) toll-free at 1-800-526-2839. Information may also be requested through its website at *http://ncrad.iu.edu*. People who are interested in joining the Neuroimaging Initiative or an AD clinical trial should contact ADEAR at *www.alzheimers.org*, or call ADEAR toll-free at 1-800-438-4380 for a referral to the nearest participating study site.

A Final Word of Caution

Because AD is such a devastating disease, caregivers and patients may be tempted by untried, unproven, and unscientific cures, supplements, or prevention strategies. Before trying pills or anything else that promises to prevent AD, people should use caution and check with their doctor first. These purchases might be unsafe or a waste of money. They might even interfere with other medical treatments that have been prescribed.

For More Information

Becoming well informed is another important thing that people can do to protect their health. Thousands of Internet websites provide health-related information, including information on AD. Some of the information on these websites is reliable, but some is not. Health websites sponsored by the Federal government are good sources of information, as are websites of large professional organizations and well-known medical schools. Some excellent Internet sources of AD and other health-related information for consumers are:

National Institute on Aging Information Center

P.O. Box 8057
Gaithersburg, MD 20898-8057
1-800-222-2225
www.nia.nih.gov

NIA offers many helpful publications, including *Online Health Information: Can You Trust It? Life Extension: Science Fact or Science Fiction? Pills, Patches, and Shots: Can Hormones Prevent Aging?*

Each can be viewed and ordered at:

www.niapublications.org.

Alzheimer's Disease Education and Referral (ADEAR) Center

P.O. Box 8250
Silver Spring, MD 20907-8250
1-800-438-4380
www.alzheimers.org

This service of the NIA offers information and publications on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to AD. *Alzheimer's Disease: Unraveling the Mystery*, for example, uses easy-to-understand text and illustrations to explain AD, highlight ongoing research, and describe efforts to support AD caregivers. *The Progress Report on Alzheimer's Disease* provides a more comprehensive update on NIH's AD research effort. These and other ADEAR publications can be previewed and ordered on the website. ADEAR staff also respond to information requests and make referrals to local and national resources. ADEAR also maintains a database of AD clinical trials.

Alzheimer's Association

225 N. Michigan Avenue, Suite 1700
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1-800-272-3900
www.alz.org

This nonprofit association supports families and caregivers of patients with AD and funds AD research. Chapters nationwide provide referrals to local resources and services, and sponsor support groups and educational programs.

For additional copies of this publication or further information on Alzheimer's disease, please contact:

Alzheimer's Disease Education and Referral (ADEAR) Center
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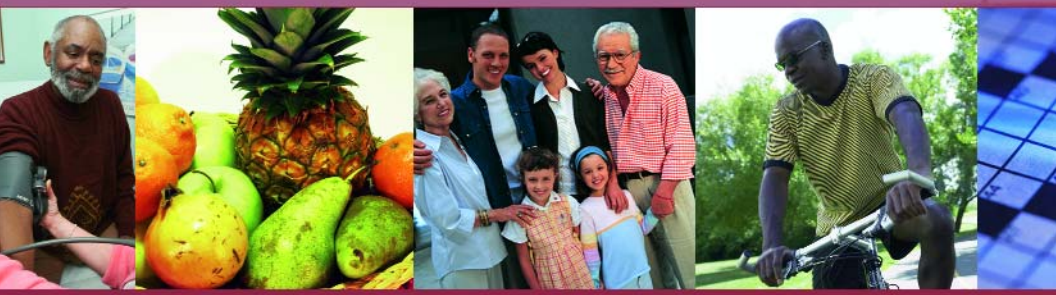

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